Nonbacterial Thrombotic Vegetations

Occurrence in Neonate, Infant, and Child, and Relation to Valvular Lesions in Cardiac Defects

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NONBACTERIAL THROMBOTIC ENDOCARDITIS is a rarity in the pediatric age group. Cases have been included in only two of the comprehensive reviews of this lesion. Allen and Sirota [1] listed 1 patient under 10 years of age, and 7 who were in the second decade of life. Eliakim and Pinchas [2] included a single case in the group 10–19 years old. There have been five case reports of nonbacterial vegetations in newborn infants,[3–7] but the lesion has not been previously described in older infants.

In the adult, nonbacterial thrombotic endocarditis has been associated with a variety of conditions, but it has been noted with particular frequency as a syndrome with mucin-producing tumors and venous thrombosis.[8] Recognition of the entity has been stressed because the vegetations may be the source of lethal embolization.[1,9,10] Emboli from vegetations have also been described in infants, but their significance has been more difficult to assess.[4–7,11]

We have collected 27 cases of nonbacterial thrombotic endocarditis in the pediatric age group, including 2 additional cases in infants who died during the neonatal period. This report reviews the observations at necropsy in these cases and demonstrates a previously unrecognized association with congenital heart disease in over half the patients. Observations on a small control group of children with nodular valves are also included.

Material and Observations

Twenty-seven cases of nonbacterial thrombotic endocarditis occurring in infancy and childhood were uncovered by a review of over 200 patients with a variety of valvular lesions listed in the index of the necropsy files of The Johns Hopkins Hospital. The gross descriptions

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Table 1. Nonbacterial Thrombotic Vegetations in Neonates, Infants, and Children

Pt.	Age	Vegetations: Site: Right	Vegetations: Site: Left	Vegetations: Age	Emboli: Heart	Emboli: Lungs	Other thrombi	Other data
				Group A—Neonates				
1	27 hr.	Tricuspid	Mitral	Fresh	Pres.	Pres.	—	Intrauterine distress; massive pulmonary hemorrhage; occasional hyaline membranes
2	11 days	Tricuspid	—	Fresh	Pres.	Pres.	Portal vein; sup. VC; RA	Truncus arteriosus; VSD; multiple congenital G.I. malformations; recent repair of tracheo-esophageal fistula; duodenojejunostomy for duodenal atresia
				Group B—Infants & Children Without Cardiac Defects				
3	3 mo.	—	Mitral	Fresh	Pres.	Pres.	RV	History of respirator therapy; pneumonia (viral?); hyaline membranes
4	3 mo.	—	Mitral	Fresh	Pres.	Pres.	Splenic venules	History of respirator therapy; fresh pneumonia; hyaline membranes
5	4 yr.	Tricuspid	—	Fresh & organizing	—	Pres.	—	Ruptured appendix; peritonitis; history of respirator therapy; hyaline membranes; recent laparotomy
6	7 yr.	—	Mitral	Fresh	—	—	—	Cranial exploration with secondary infection; emboli in abdominal aorta & intrarenal arteries
7	13 mo.	Tricuspid	Mitral	Fresh	—	—	—	Leukemia, acute
8	3 yr.	Tricuspid	Mitral, aortic	Fresh	—	—	—	Leukemia, acute
9	10 yr.	—	Aortic	Fresh	—	—	—	Leukemia, subacute lymphoid; pneumonia; membranous colitis
10	10 yr.	Tricuspid	Mitral	Fresh	Pres.	—	—	Systemic periarteritis; ruptured appendix; peritonitis; recent laparotomy
11	14 yr.	—	Mitral	Fresh & organizing	—	Pres.	Inf. VC; adrenal & meningeal veins	Chronic nephrosis; perforated duodenal ulcer; peritonitis

VC indicates vena cava; RA, right atrium; RV, right ventricle; and VSD, ventricular septal defect.

and available gross and histologic material on these patients were reviewed, and the material was segregated into three categories. The 2 neonatal patients, comprising Group A (Table 1), are described in detail since they represent the sixth and seventh examples of this entity. Group B (Table 1) consists of older infants and children with no cardiac defects, ranging in age from 3 months to 10 years. The 16 patients with infundibular or pulmonary valve stenosis are described together to illustrate their similarity (Table 2). The data on 8 additional patients, without vegetations but with distorted valves, are summarized in Table 3.

Bacterial cultures and stains were negative on all the valvular lesions; the morphology of the vegetations also precluded a possible bacterial etiology. In many cases clinical and/or postmortem blood cultures were also available and showed no growth. The single exception was Patient 5 from whom *Pseudomonas* was grown from the postmortem blood. Foci of infection were demonstrated in this and 7 other patients as listed by diagnosis under *Other data* in the tables.

In each instance, the vegetations had the histologic appearance of bland thrombi with a varying proportion of platelets and fibrin. They were usually acellular and in no case was a purulent infiltrate present. The freshest vegetations were bulky, with a distinct thrombus structure; in others the elements of the vegetation were more compact and hyaline.

Continuity between vegetations of recent origin and the valve was demonstrated in only 2 patients, and degenerative changes in the valve collagen with necrosis at the site of attachment was seen in both. The vegetations were older with organization beginning at the base in 15 of the 27 patients, including 13 of the 16 with cardiac defects. Foci of calcification were found in six of the organizing vegetations in the latter group.

The site of the vegetations was as follows: tricuspid valve, 11; pulmonic, 11; mitral, 10; and aortic, 3. This includes 7 patients with lesions on more than one valve. In four instances of infundibular stenosis, the vegetations were adherent to the endocardium of the outflow tract, as well as to the valve. Right-sided vegetations predominated in patients with congenital cardiac malformations (16 of 19), whereas in the children with otherwise normal hearts, two-thirds of the vegetations were in the left side of the heart (10 of 15).

Cysts of Luschka were seen on nine valves, with seven on the mitral and two on the tricuspid valve in seven hearts. Vegetations were also found on five of these valves, but were superimposed on the blood cyst only in Patient 1.

Pulmonary emboli were noted in 17 of the patients and usually in association with vegetations in the right heart (Table 1). In Patients 3 and 4, there was no evidence of a valvular lesion in the right heart at necropsy, and the pulmonary emboli probably came from the mural thrombus in the right ventricle or venous thrombi. Coronary emboli were found in 5 patients. In four, their source was a left-sided vegetation; in Patient 2, emboli from the tricuspid valve could have passed through the ventricular septal defect, or directly into the truncus from which the coronary arteries were derived. In Patient 7 there was a mitral vegetation, and resulting emboli were present in the aorta and renal arteries; both kidneys showed multiple fresh infarcts. Renal, aortic, and iliac artery emboli were also present from tricuspid vegetations in Patients 14 and 17 with tetralogy of Fallot. In Patient 14, ischemic gangrene of the leg had developed; in Patient 17, small emboli were also noted in the spleen and liver. Infarcts were also seen in the heart (Patient 3) and lungs (Patient 18). Venous thrombosis was an additional finding in Patients 2, 4, and 11. A history of recent operation was present in 15 of the 27.

Neonatal Patients

Patient 1 was a term, white male weighing 3130 gm. Midforceps delivery was necessary because of intrauterine distress and a bradycardia of 80. The infant was dusky at birth and rapidly became cyanotic, with a heart rate greater than 200/min. In spite of digitoxin and antibiotic therapy, the baby survived only 27 hr. The necropsy revealed no infection, but anoxia was indicated by massive alveolar and interstitial pulmonary hemorrhage. There was also slight hyaline membrane formation and a few aspirated squames. Cysts of Luschka and fresh vegetations were present on the mitral and tricuspid valves, but overlaid the cyst only on the tricuspid valve (Fig. 1A). Fibrin stains demonstrated a network of fibrin with masses of consolidated platelets in the vegetations (Fig. 1B). Numerous small, fresh emboli were found in sections of the lungs and myocardium in this infant.

Patient 2 was a premature, white female with a birth weight of 1758 gm. A tracheo-esophageal fistula with esophageal atresia was repaired on the third day of life; 4 days later, a duodenojejunostomy was performed for duodenal stenosis. The infant's death on the eleventh day of life resulted from a pneumohydrothorax that developed from necrosis in the distal esophageal stump. At necropsy, cardiac defects—ventricular septal defect with truncus arteriosus—were also demonstrated. There were cysts of Luschka on the mitral and tricuspid valves, and a compact but fresh vegetation was lodged on the tricuspid valve (Fig. 2). Fresh thrombi were present in the right atrium, superior vena cava, and portal vein. Small emboli, similar in structure to the tricuspid vegetation, were found in the myocardium and lungs.

Older Infants and Children Without Cardiac Malformations

The patients in Group B showed a diversity of diagnoses. Patients 3 and 4 were 3-month-old infants with mild upper respiratory infections; these infants died

unexpectedly. An artifical respirator was used in both cases; Patient 3 survived 4 days, but Patient 4 only about 2 hr. Hyaline membranes were present in the lungs of both; in addition, Patient 3 had mild, diffuse interstitial pneumonia, and Patient 4, an area of lobular pneumonia in the right lung. Fresh nonbacterial vegetations were found on the mitral valves; a cyst of Luschka in Patient 4 was in a different segment of the mitral valve from the vegetation (Fig. 3).

Patients 5 and 6 both died after operation: Patient 5, shortly after laparotomy for ruptured appendix and peritonitis. There had been postoperative respirator therapy, and the lungs contained hyaline membranes. Although sepsis was present, the tricuspid vegetation was fresh and sterile. Patient 6 underwent cranial exploration because of hydrocephalus. Wound infection followed, and a brain abscess at necropsy contained gram-negative bacilli. The organizing vegetation on the mitral valve was sterile.

Patients 7, 8, and 9 were children with acute leukemia. Patients 7 and 8 had multiple fresh vegetations in both sides of the heart, and Patient 9 on the aortic valve only. There were no emboli. A cyst of Luschka, filled with leukemic cells, was noted on the mitral valve of Patient 8.

In Patient 10, there had been a chronic febrile illness and at necropsy there was a massive distribution of systemic periarteritis nodosa; the hyaline, nonorganized vegetation was of the Libman-Sacks variety. Patient 11 had had a long history of steroid therapy for nephrosis with azotemia. Sepsis complicated perforation of a duodenal ulcer. The mitral vegetation showed considerable organization (Fig. 4).

Patients with Infundibular and Pulmonary Valve Stenosis

The 16 children in Table 2 ranged in age from 1 month to 14 years. Thirteen patients had a typical tetralogy of Fallot; 2 had "pure" pulmonic stenosis, and in one the pulmonic lesion was associated with tricuspid atresia and hypoplasia of the right ventricle. Vegetations were found in the right heart in every patient except Patient 27; in 2 patients, additional vegetations were present on the mitral valve. Only 3 patients had completely fresh vegetations devoid of organization or calcification. The age of the vegetation was not related to the patients' ages, which were scattered at 10 months, and 3 and 9 years, or to a history of cardiac surgery. The majority of the vegetations in this group appeared older, but even when organization was advanced, the intrinsic thrombus structure was present in the superficial portion of the vegetation (Fig. 5). Focal calcification was present in 5 patients (Fig. 6).

Pulmonary emboli were seen in 12 of the 16 patients; in Patient 18 fresh lung infarction had occurred. Systemic emboli were found in 2 patients: Patient 14 had emboli in the abdominal aorta and iliac arteries, and Patient 17 had visceral emboli. There was a history of polycythemia in all 16 patients. Cysts of Luschka located on the mitral valve and unrelated to the vegetations were noted in Patients 12, 18, and 20.

In 11 of the 16 children there was a history of recent cardiac operation; death occurred during operation in four, and from several hours to 12 days later in the remaining seven. In Patient 16, pneumonia was a postoperative complication; in Patient 17, respirator therapy was given and the lungs contained hyaline membranes. A subclavian-pulmonic anastomosis had been made 6 years before death in Patient 26; no operation had been performed on the remaining four patients.

Patients with Nodular Sclerosis of Heart Valves

In reviewing pediatric cases for nonbacterial vegetations, another type of lesion was found in 9 infants and children with cardiac malformations; the ages of the

Table 2. Nonbacterial Thrombotic Vegetations in Patients with Congenital Cardiac Defects

Pt.	Age	Vegetations: Site: Right	Vegetations: Site: Left	Vegetations: Age	Cardiac malformation	Emboli: Lungs	Emboli: Other	Recent operation	Other data
12	1 mo.	Tricuspid	—	Fresh, organizing, calcific foci	PPS	Pres.	—	—	Hgb 16.5 gm.
13	10 mo.	Pulmonic	—	Fresh	PPS	—	—	—	Hct 34; sickle cell anemia
14	17 mo.	Tricuspid, pulmonic	—	Fresh & organizing	T/F	—	Aorta, iliacs	—	Hgb 13 gm.; RBC 7,300,000
15	19 mo.	Pulmonic	—	Fresh & organizing	T/F	Pres.	—	Yes	—
16	2 yr.	Pulmonic	—	Fresh & organizing	T/F	Pres.	—	Yes	Hydrocephalus; pneumonia
17	3 yr.	Tricuspid	—	Fresh	T/F	Pres.	Spleen, liver, kidneys	Yes	History of respirator therapy; pulmonary hyaline membranes
18	3 yr.	Pulmonic	—	Fresh, organizing, calcific foci	T/F	Pres.	—	Yes	Congenital rubella; Hgb 20 gm.
19	4 yr.	Tricuspid	Mitral	Fresh & organizing	T/F	Pres.	—	Yes	Hct 78
20	4 yr.	Pulmonic	—	Fresh, organizing, calcific foci	T/F	Pres.	—	Yes	Hct 77
21	5 yr.	Pulmonic	—	Fresh & organizing	T/F	Pres.	—	Yes	Hct 65
22	6 yr.	Pulmonic	—	Fresh & organizing	PPS; tricuspid atresia	—	—	—	Hgb 20 gm.; RBC 7,600,000
23	6 yr.	Pulmonic	—	Fresh, organizing, calcific foci	T/F	Pres.	—	Yes	Hct 88
24	6 yr.	Pulmonic	—	Fresh, organizing, calcific foci	T/F	Pres.	—	Yes	—
25	7 yr.	Pulmonic	Mitral	Fresh & organizing	T/F	Pres.	—	Yes	Hgb 25 gm.
26	9 yr.	Tricuspid	—	Fresh	T/F	—	—	—	Hgb 13.9 gm.
27	14 yr.	—	Aortic	Fresh & organizing	T/F	Pres.	—	Yes	Hgb 23.5 gm.; RBC 10,500,000

PPS indicates pure pulmonic stenosis; T/F, tetralogy of Fallot.

children ranged from 1 week to 14 years. This lesion consisted of grossly nodular thickening of the valves associated with gross distortion (Table 3). No vegetations or thrombi were present in these hearts.

In Patient 28 the bulbous tricuspid and pulmonic valves were composed of a mixture of vascular connective tissue containing focal calcification with hypocellular myxoid foci (Fig. 7). The enlarged valves of Patient 32 were similar, but contained no calcification. The redundant tricuspid and mitral valves of Patient 30 showed a uniform myxomatous stoma that resembled embryonic connective tissue (Fig. 8). The altered valves of the remaining patients showed less marked enlargement, but were similar in structure and embryonic appearance.

Comments

Nonbacterial vegetations are now appreciated as an important necropsy finding, both as a source of emboli [1,9] and because of their vulnerability as a nidus for bacterial endocarditis; [12] yet there is no agreement as to their etiology or pathogenesis. Although frequently associated with neoplasms, congestive failure, and venous thrombosis, the vegetations have also been found following acute illnesses and in the immediate postoperative period. Allen and Sirota [1] have stressed the degenerative nature of the lesions in the majority of their patients because of the presence of swollen valvular collagen and occasional Anitschkow myocytes. Other observers, however, have interpreted the vegetations as thrombi because of their prominent fibrin and platelet architecture, although these thrombi may form on previously damaged valves.[9,10,13]

The present study indicates that nonbacterial vegetations may also be found in infants and children, and may occur in diverse conditions, both acute and chronic. Emboli occurred in 20 (74%) of these 27 pediatric patients, but the significance of these emboli was more difficult to evaluate than those found in adults.

The vegetations in newborn infants are of interest not only because they are unusual in the neonatal period, but because of the frequency of valve cysts at this age.[14] In the 5 patients previously reported,[3–7] death occurred within the first 48 hr.; the vegetations were fibrinous, and in 4 of the 5, were found on the tricuspid valve. Emboli were present in the lungs in 4 patients and in the systemic circulation of 2. Cysts of Luschka were identified twice, but in only one heart were cyst and vegetation present on the same valve.

There are 2 newborn infants in the present series and the vegetations and distribution of resulting emboli in each are similar to those in the previous reports. Cysts of Luschka were identified in both hearts, as they were in the hearts of the remaining 3 infants who were under 4 months of age; however, the cysts appeared to have no etiologic significance, since only in the first patient was the cyst located near a

vegetation. There was no indication of the etiology of the vegetations in this 27-hr. infant. The history of intrauterine distress and the massive pulmonary hemorrhage at necropsy are indications of stress [15] but are common findings. The other neonate survived longer and resembled the older infants because of the multiple congenital malformations (including truncus arteriosus) and the history of recent surgery.

In pediatric age groups, as in the adult groups, the pathogenesis of the nonbacterial vegetations is unclear. Endothelial damage was demonstrated in only a few of the fresh lesions. The collagen in older, organizing lesions could not be differentiated from that in the underlying valve structure, yet this end-stage appearance could easily represent organization of a thrombus or a previously injured valve. The endothelial covering of the older lesions is also nonspecific. Nevertheless, Anitschkow myocytes were frequently identified in the organized lesions, and since their presence is usually synonomous with myocardial tissue,[16] they suggest repair in the valve rather than thrombus organization.

A possible relation may exist between organization of the vegetations and the sclerotic nodules seen in the valves of the patients in Table 3. Oka and Angrist [13] noted that healing of vegetations may result in nodular distortion of the valves. In Patients 28 and 32, vascular granulation tissue illustrates repair, and the focal calcification in Patient 28 indicates previous necrosis. Since Patient 28 was a newborn infant, the healing of the valvular lesions must have occurred in utero, but at necropsy the distorted valves appeared to be a congenital malformation. In contrast, the structure of the distorted valves of Patient 30, aged 2

Table 3. Distorted Valves in Congenital Cardiac Malformations

Patient	Age	Distorted valves		Cardiac malformations*	Other data
		Right	Left		
28	1 wk.	Pulmonic; tricuspid		T/F	
29	45 day		Mitral	VSD	
30	2 mo.	Tricuspid	Mitral	PDA; ASD; hypoplasia aorta	
31	3 yr.		Mitral	T/F	Congenital rubella
32	4 yr.	Pulmonic		PPS; PFO; PDA	
33	5 yr.	Pulmonic		T/F	Recent operation
34	11 yr.	Pulmonic		T/F	Recent operation; pulmonary emboli
35	14 yr.	Pulmonic; tricuspid		T/F	Recent operation

* T/F, tetralogy of Fallot; VSD, ventricular septal defect; ASD, auricular septal defect; PPS, pure pulmonic stenosis; PFO, patent foramen ovale PDA, patent ductus arteriosus.

months, consisted of embryonic tissue and was a malformation of unknown etiology. The etiology of the malformed valves in the older children with congenital cardiac disease could not be distinguished on the basis of morphologic characteristics.

Congenital cardiac malformations were present in 17 of the 27 patients with nonbacterial vegetations (Patient 2 in addition to the patients in Table 2); this is interesting in several respects: It indicates that altered hemodynamics are an important factor in the production of the vegetations, a supposition supported by the presence of vegetations following experimental AV fistula.[13] Furthermore, in our patients the pulmonary outflow tract was deformed in every case, and the vegetations were on the pulmonary valve in 11 patients and in the right heart in all but one. The frequency and incidence of this association, however, is unknown since this was a selective review, and cardiac malformations are a relatively common finding in the pediatric necropsy population of a referral hospital. Finally, the findings in a small sample of adults with similar malformations indicate that the vegetations are related to the cardiac defect rather than to the age of the patient.

It is difficult to assess the role of an alteration of the clotting mechanism in the production of the vegetations, as laboratory studies were not usually available. However, it is noteworthy that the red cell volume was elevated in nearly every patient with a cardiac defect, and that ecchymoses and larger hemorrhages were present in the infant with neonatal anoxia and in the 3 patients with leukemia.

Multiple venous thromboses have been noted frequently in adults with nonbacterial vegetations,[8] and a fibrinous vegetation was described in a baby with widespread venous thrombosis.[7] In the present series venous thrombosis was noted twice following recent operation and once in an infant with pneumonia and hyaline membranes, possibly a result of oxygen toxicity.[18,19] Hyaline membranes in these and in 4 additional patients may, in addition, be an indication of a possible clotting defect.[20]

Lung emboli were present in 13 of the patients with cardiac defects and 5 of the remaining 10; coronary emboli were present in 5. Other sites of embolus formation were infrequent and of less certain significance. In 8 patients foci of infection and/or sepsis was demonstrated at necropsy, but there was no evidence that the vegetation might be a manifestation of a Shwartzman-like reaction or the direct result of infection.[17]

The findings in the patients with cardiac malformations and elevated hematocrits suggest that altered hemodynamics are an important factor

in the development of valvular lesions. In the remaining patients, it is apparent that numerous nonspecific factors may contribute to the pathogenesis of the nonbacterial vegetations.

Summary

Twenty-seven cases of nonbacterial thrombotic vegetations were found during a selected review of pediatric necropsies. Two infants had died during the neonatal period, and the remaining infants and children had been 3 months to 14 years of age at death. Pulmonary and systemic emboli were found in 20 patients (74%).

In 17 cases the vegetations were present in patients with cyanotic congenital heart disease. All of the defects included anomalies of the pulmonary outflow tract, and in all but one of these, the lesions were in the right side of the heart.

The vegetations had the structure of bland thrombi, and in many, showed organization at the base. Well organized lesions resembled the nodular distortion of the valves that were seen in 8 children with congenital cardiac malformations. The association of vegetations with cyanotic congenital anomalies and elevated hematocrits suggest that altered hemodynamics may be an important factor in the pathogenesis of the lesions.

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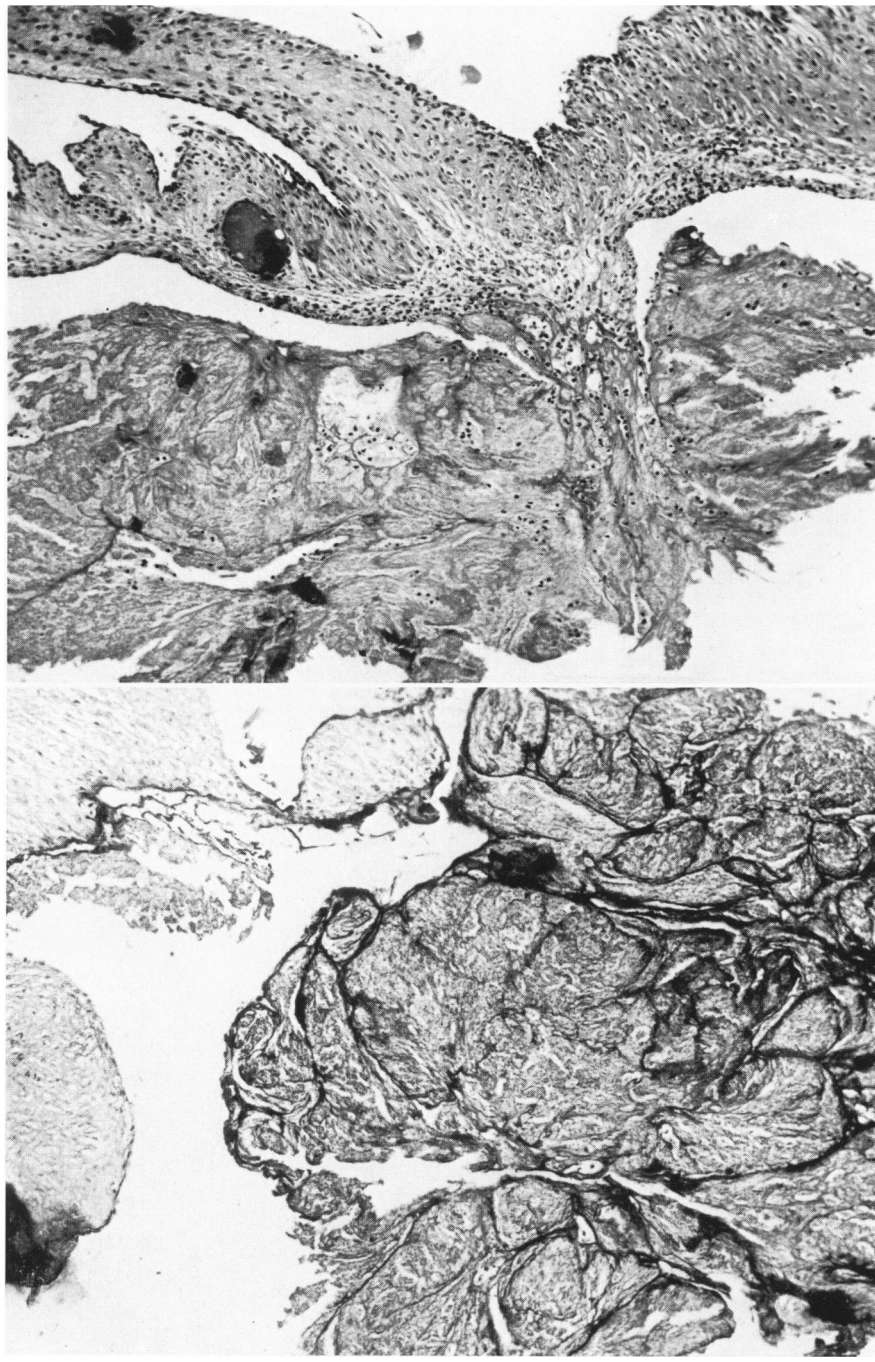
The photomicrographs were prepared by Raymond Lund.

[*Illustrations follow*]

Legends for Figures

All sections shown in photomicrographs were stained with hematoxylin and eosin unless otherwise indicated.

Fig. 1 A. Tricuspid valve of Patient 1, who died at 27 hr. Vegetation is adherent to a focus of endothelial degeneration and adjacent to cyst of Luschka. Similar vegetation was present on mitral valve. × 100. **B.** High magnification of fibrin stain of same lesion shows its typical thrombus structure with fibrin network and columns of coalesced platelets. MacCallum-Goodpasture. × 300.



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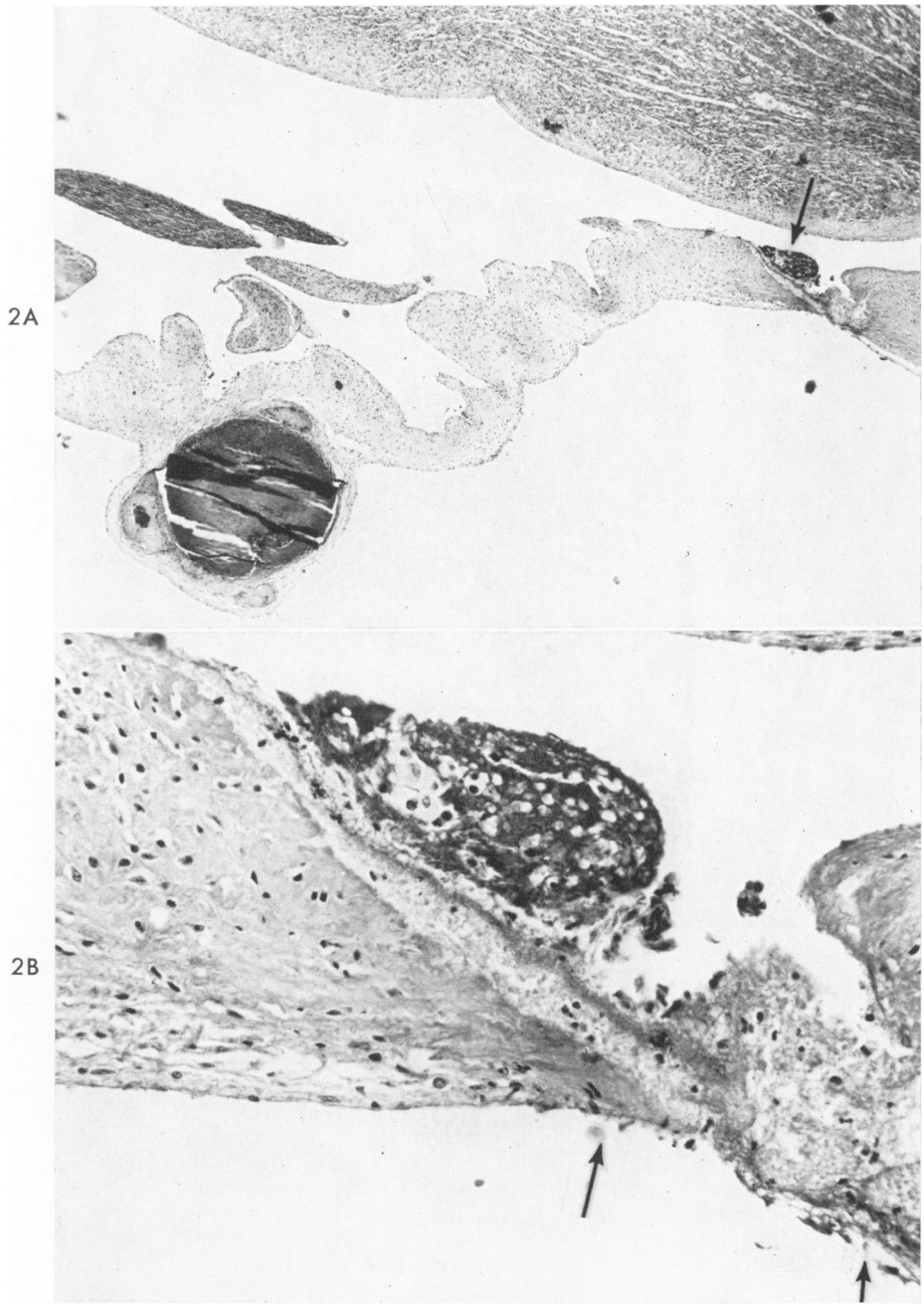
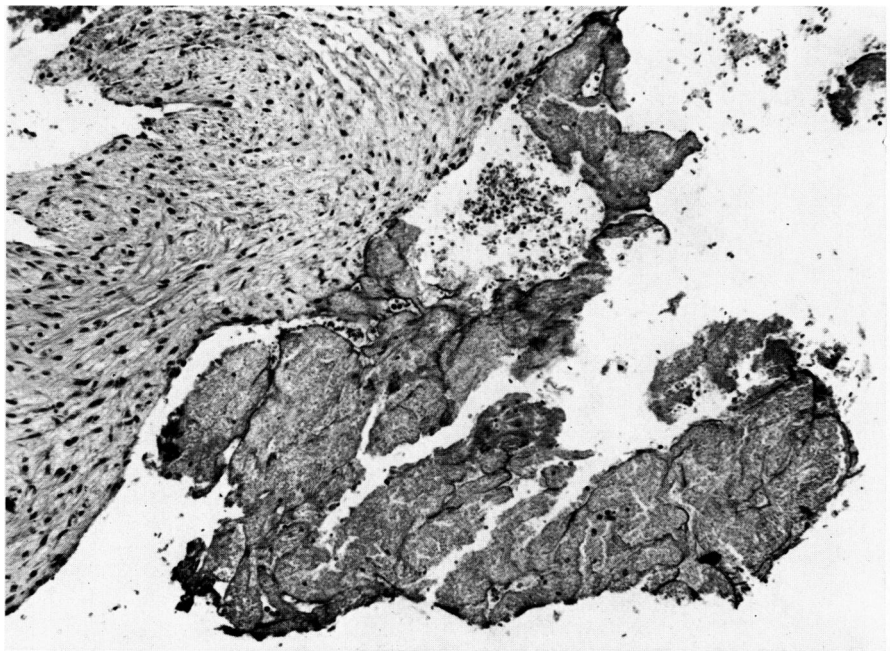


Fig. 2 A. Tricuspid valve of Patient 2, who survived 11 days. There is a large cyst of Luschka. Only a small, fresh vegetation remains adherent to valve (*arrow*), but pulmonary emboli were present. × 35. **B.** High magnification of vegetation illustrating its compact thrombus structure. Necrosis in valve can be seen between arrows and extends beneath vegetation. × 300.



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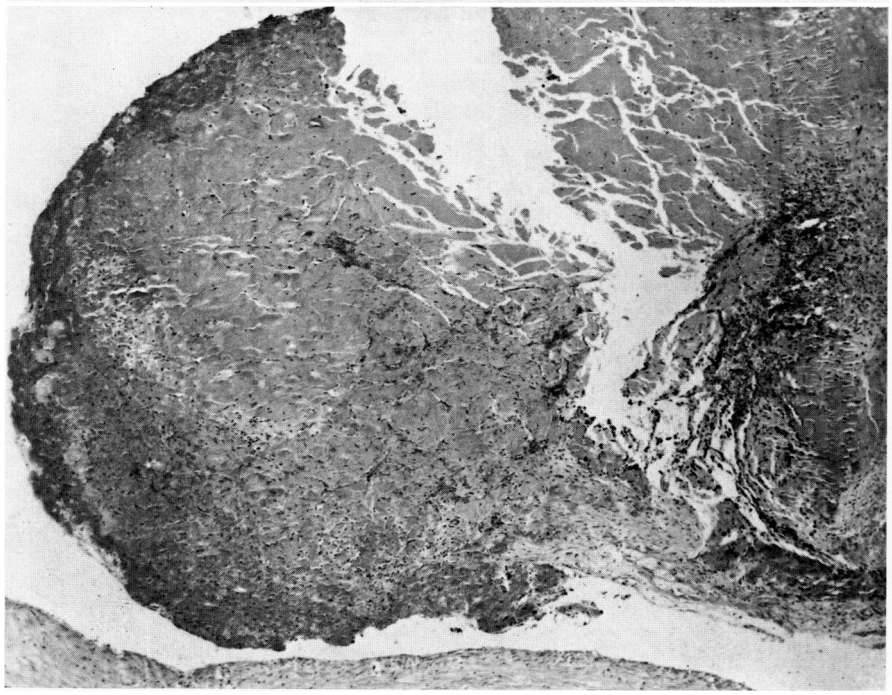

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Fig. 3. Mitral valve of Patient 3, who died unexpectedly at 3 months. Fresh thrombotic vegetation is loosely adherent to an apparently normal valve. × 120. **Fig. 4.** Older vegetation (Patient 11, 14 years old) with organization on superior surface of mitral valve (*right*). Auricular endocardium can be seen at bottom. History of patient included chronic, steroid-treated nephrosis, with terminal peritonitis from a ruptured duodenal ulcer. × 45.

Fig. 5. Organizing vegetation from 17-month-old child with tetralogy of Fallot (Patient 14), showing granulation tissue extending from valve into the thrombus and obliterating outline of valve. Fresh thrombus material is visible at lower margin. Large emboli were present in aorta and iliac arteries. × 45.

Fig. 6. Pulmonic valve of Patient 20, a 4-year-old child with tetralogy of Fallot. Valve is distorted by an organizing and partly calcified vegetation; bulky, fresh thrombus structure can be noted in lower half of photomicrograph. × 45.

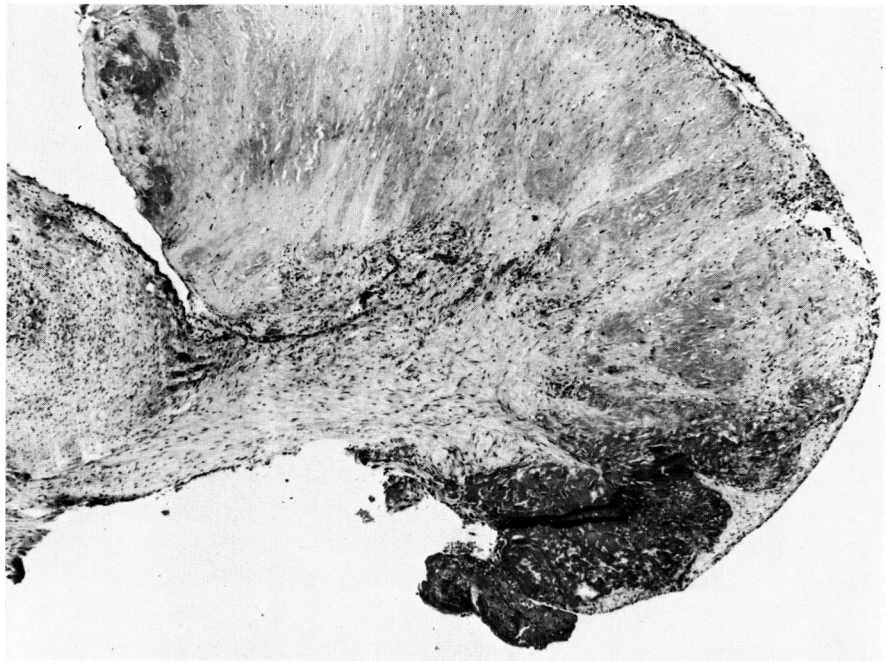

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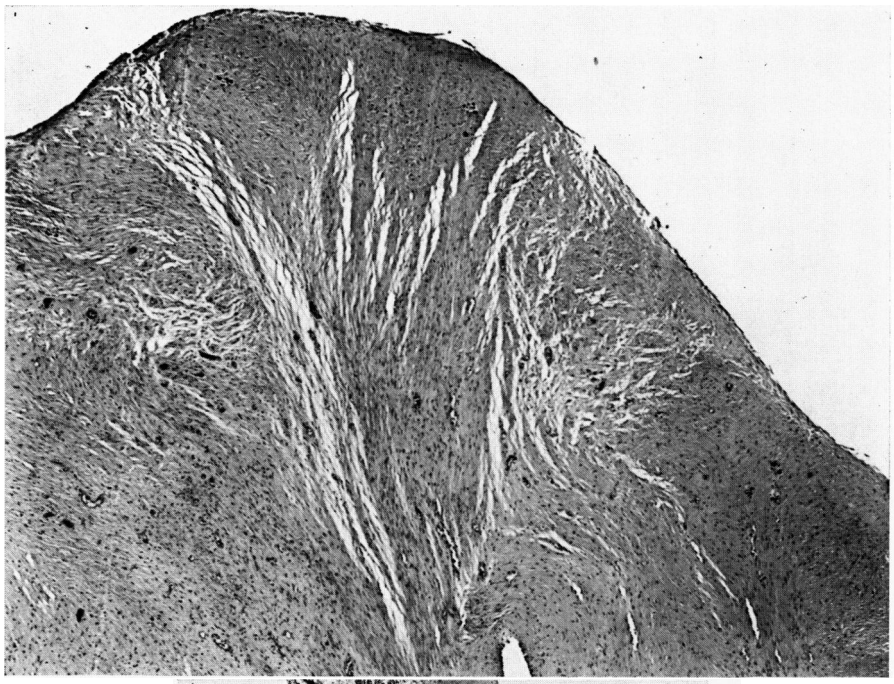
Fig. 7. Part of bulbous tricuspid valve from 1-week-old infant with tetralogy of Fallot (Patient 28); there is granular calcification embedded in hypocellular, vascular, connective tissue stroma. × 35.

Fig. 8. Redundant tricuspid valve of Patient 30, a 2½-month-old infant with multiple cardiac defects, is composed of connective tissue with a prominent fetal appearance. × 8.



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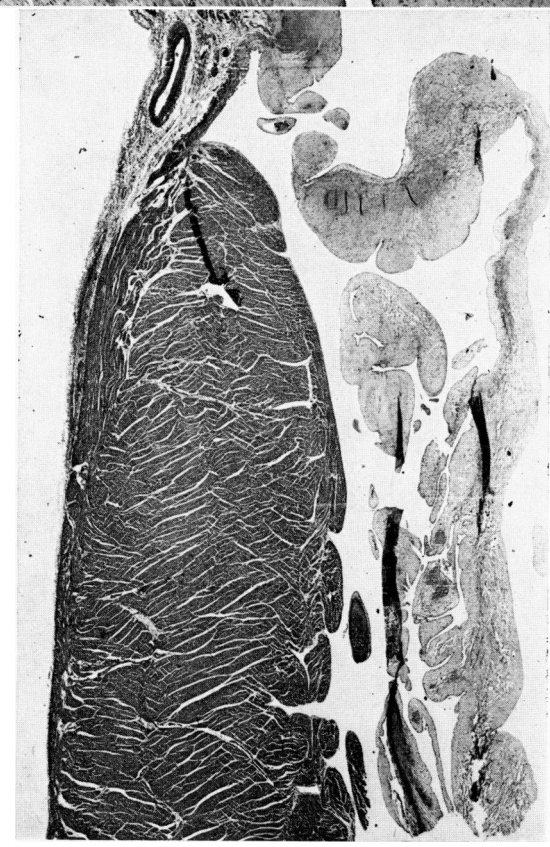

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